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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,903	12/08/2004	Catharina Svanborg	2491-49	7669

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EXAMINER	
ROOKE, AGNES BEATA	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/506,903	SVANBORG ET AL.	
	Examiner	Art Unit	
	Agnes B. Rooke	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 06/14/05; 09/07/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-15 are pending. Claim 16 is cancelled.

This application is a 371 of PCT/IB03/01293, filed on 03/07/2003, which claims priority to UNITED KINGDOM 0205347.8, filed on 03/07/2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 5, 6, 9, and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claims 1, 4, and 9, the Applicant refers to a fragment of α-lactalbumin. These claims do not satisfy the written description requirement because the fragments do not have a necessary function, since these fragments do not have intrinsic characteristics by themselves. Thus, the structure of the fragments does not correspond with their function(s).

Also, claim 1, refers to a fragment of a variant of α-lactalbumin. The variant of the α-lactalbumin is not disclosed and thus unknown, therefore a fragment of a variant of α-

lactalbumin is also unknown, and the structure of the variant does not correspond with its function.

In claim 1, the Applicant refers to a biologically active complex comprising α-lactalbumin or its variants or its fragments, and a cofactor which stabilizes that complex, where the cofactor is other than C:18:1:9 cis fatty acid. On page 51 of the specification, lines 20-29, the Applicant refers to Figure 1, which shows simplified fatty acid structures that were investigated for their ability to produce a HAMLET like molecular complex. However, no examples of cofactors, other than C:18:1:9 cis fatty acid are presented in the claim. Therefore, the structures of other cofactors should be provided, otherwise the structure of undisclosed cofactors do not correspond with their function.

In claims 1, 4, 5, 6, 9, 10, the Applicant refers to variant of α-lactalbumin. The variants are not disclosed, and thus the structure of the variants does not correspond with their function and the written description requirement is not satisfied.

In claim 9, an appropriate SEQ ID NO should be provided in the claim to examine the claim accordingly.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 5 refer to "different fatty acid with a similar configuration" which is indefinite because there are undisclosed numbers of fatty acids with cis or trans configurations.

In claims 7 and 9, the Applicant refers to a complex which "comprises a fragment of α-lactalbumin or a variant thereof, and where the fragment includes the entire region from amino acid 34-86 of the native protein." However, a SEQ ID NO that would provide reference to the claimed positions of amino acids 34-86 is not provided, and thus the claim is indefinite. Thus, the appropriate SEQ ID NO must be provided in the claim, since specific amino acid positions are claimed in reference to an unknown SEQ ID NO.

In claim 12, the name of an "S70R" mutation must be fully spelled out. Further, there is no reference to S70R in the specification, thus the claim cannot be adequately searched. Also, claim 12 should depend from claim 10.

In claim 15, a conclusionary statement regarding the end point for the treatment should be provided, such as that the cancer is treated after administration of the complex of claim 1. Also, the method must further explain how the administration of the complex occurs to cancer cells.

However, the claim 15 would still be indefinite, since the structure of the complex from claim 1 cannot be ascertained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

On page 4225, top right paragraph, HAMLET was shown to induce apoptosis in several human and murine tumor cell lines, including Jurkat and L1210 leukemia cell lines, the A549 lung carcinoma, and A-498 kidney carcinoma, where native α-lactalbumin had no effects on these cells; where the conversion was achieved with α-lactalbumin derived from human milk whey and with recombinant protein expressed in E.coli; and where it can be suspected that molecules like HAMLET can aid in lowering the incidence of cancer in breast-fed children. See Abstract, and page 4226, right paragraph (Claim 15 of the instant invention).

Claim 13 is included in this rejection because it states that the complex further comprises calcium atoms. Swensson et al. state that the binding of calcium is reduced or that calcium ions are released from the configuration, but the reference never excludes completely calcium ions that could be present in the complex.

Claim 14 is included in this rejection because a pharmaceutically acceptable carrier could be a molecule water, for example.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 10, 11, and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Swensson et al., Conversion of α-lactalbumin to α-lactalbumin a protein inducing apoptosis, PNAS (April 11, 2000), vol.97, no.8, p. 4221-4226.

Swensson et al. on pages 4223-4, teach that the conversion of α-lactalbumin to the apoptosis-inducing form involved a cofactor from casein; where α-lactalbumin was converted from the regular, native state to a folding variant with altered biological function (Claim 1), where the variant was shown to induce apoptosis in tumor cells and immature cells (claim 15); where conversion to HAMLET (human α-lactalbumin made lethal to tumor cells) required partial unfolding of the protein and a specific fatty acid, C18:1, as a necessary cofactor (Claims 1, 2, 3, 10 of the instant invention). See pages 4223-4; Figures 1-3; and Abstract. Also, on page 4225, *Discussion* section, the conformation of HAMLET was achieved by changing the conformation of α-lactalbumin from the native to a partially unfolded state by using EDTA treatment because it releases the calcium ions (Claims 1-6 of the instant invention). (This reference would apply to claims 1-6 of the instant invention, because C18:1 fatty acid could be represented by C18:1:11 and not necessary C18:1:9).

α-lactalbumin from human milk whey and recombinant protein was shown to convert to the active complex only on the C:18:1 fatty acid-preconditioned column and only when applied in the apo form. See page 4224, bottom right paragraph. (Claims 1-6 and 10-11of the instant invention).

Claims 1 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swensson et al., Conversion of α-lactalbumin to α-lactalbumin a protein inducing apoptosis, PNAS (April 11, 2000), vol.97, no.8, p. 4221-4226 in view of Permyakov et al., Mutating aspartate in the calcium-binding site of α-latalbumin: effects on the protein stability and cation binding, Protein Engineering, vol.14, No.10, pp. 785-789, 2001.

The teachings of Swensson et al. are disclosed above. Swensson et al. does not teach mutations in α-lactalbumin.

Permyakov et al. teach measurements of Ca(II) affinity of mutants of α-lactalbumin, where mutants D87A and D87Nα-lactalbumin are unable to bind calcium ions. See page 785, middle of the right paragraph.

On page 786, recombinant proteins D87A and D87Nalpha-lactalbumin were expressed in E.coli, and as a consequence of protein expression, the recombinant protein contained extra methionine residue on N-terminus, which is known to destabilize α-lactalbumin; and where α-lactalbumin with D87 N mutation was unable to fold properly or bind calcium ions (Claims 7 and 8 of the instant invention).

Therefore, it would have been obvious to one of an ordinary skilled in the art at the time the invention was made to design a mutated α-lactalbumin where calcium binding site has been modified, so that the affinity for calcium is reduced as taught by Permyakov et al. and combine these with teachings of Swensson et al. that teach a composition of α-lactalbumin and a cofactor with altered calcium binding ability.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnes Rooke whose telephone number is 571-272-2055. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information about the PAIR system, see http://pair-direct.uspto.gov. or call 866-217-9197.

AR

ROBERT A. WAX
PRIMARY EXAMINER